Remarks

As discussed herein, Applicants respectfully request reconsideration and withdrawal of the objections and rejections of record.

Preliminary Matters

The Examiner is thanked for acknowledging Applicants' claim of priority to U.S. Provisional Patent Application No. 60/258,072, filed December 22, 2000.

The rationale provided by the Examiner for maintaining the restriction requirement in its present form is illogical. For example, it is stated that the polymorphisms of the present application "have acquired a separate status in the art as demonstrated by their different classification and recognized divergent subject matter". Firstly, the present polymorphisms do NOT have different classifications, but identical classifications. Secondly, the subject matter is entirely NON-divergent. These polymorphisms are all in the exact same gene. It is respectfully submitted that the Examiner simply will not be unduly burdened by searching more than one polymorphism at a time. All that needs to be done is to search for the gene as a whole, and then determine if each of the sequences found contains any one or more of the listed polymorphisms.

Amendments to the Specification

Amendments to the specification at pages 30-31 are submitted herewith. Applicants respectfully request entry of these amendments. The amended language is supported by the original specification and claims, since it is merely a deletion of browser-executable code from the specification.

Objections to the Drawings

The Examiner is thanked for pointing out drawing errors in Figures 6 and 9. Each of the errors pointed out by the Examiner will be corrected prior to paying the issue fee for any allowed claims.

With respect to Figures 10 and 11, Applicants fail to see a basis for the objection. A proper brief description of each figure is presented on page 12, under the heading "Brief Description of the Drawings", as suggested by the Examiner. Applicants fail to see how it is inappropriate to also discuss these figures further on pages 49-50. The discussion of Figures 10 and 11 on pages 49-50 merely adds to Applicants' total description of their invention, and is not

meant to take the place of the brief description on page 12. The Examiner is respectfully requested to withdraw this objection.

Status of the Claims, and Amendment thereto

Claims 1-5 and 34-37 are pending and stand rejected by the Examiner. Claims 6-33 stand withdrawn. Claims 1 and 3 are respectfully requested to be amended as indicated herewith. Reconsideration and withdrawal of the rejection of claims 1-5 and 34-37 are respectfully requested.

Amended claims 1 and 3 add no new matter, and merely amend a couple of grammatical errors, including one pointed out by the Examiner. The Examiner is thanked for noticing and advising correction of this error.

Indefiniteness Rejection

Claims 1-5 and 34-37 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite with respect to the meaning of "insertion 307". Applicants respectfully disagree and respectfully submit that the meaning of this term is fully clear from the specification and claims as originally filed.

It is respectfully submitted that the definition of insertion 307, as given on page 28, lines 23-30, is fully definite. It is defined to occur in intron 12, and to consist of a 15 bp insertion at an exactly specified position in the CETP gene. Additionally, it is clear from the specification that the insertion of the extra 15 bp occurs in allele 2. On page 47, lines 25-28 of the specification, it is stated that "subjects had the insertion at 307 if and only if they also had one 'C' allele at SNP 565 (the V allele is the wild-type)." Moreover, on page 32 in Table 1 it is shown which variation of each locus is in each allele, type 1 or type 2. Thus, it is clear that genes lacking the 15 bp insertion at 307 are the wild-type allele 1, while those having the extra 15 bp of sequence are the mutant allele 2 genes. Thus, it is respectfully submitted that there is no need to amend the claims with respect to insertion 307 in order for them to be definite.

Thus, for the reasons detailed above, the Examiner is respectfully requested to withdraw the indefiniteness rejection of claims 1-5 and 34-37.

Enablement Rejection

Claims 1-5 and 34-37 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement for the full scope of the claims. Applicants respectfully disagree and respectfully request that this rejection be withdrawn.

Applicants submit that they have fully enabled the invention as claimed. The present claims do not involve the world of algebra, with its absolutes, but the world of statistics, in which predictions are made that are sometimes wrong, but more often are right. Claims 1-5 are directed to methods "for determining whether a subject has a modified susceptibility to cardiovascular disease", not to methods of proving that a subject will absolutely develop cardiovascular disease, as the Examiner appears to be requiring. Similarly, claims 34-37 are drawn to methods "for identifying a subject suffering from a cardiovascular disorder that would be responsive to treatment with at least one cardiovascular disorder therapeutic". Again, it is understood by those of skill in the art that this is a predictive method, and it is understood to not be 100% accurate, but to provide a physician with the ability to predict that certain patients have an increased likelihood of responding to certain therapeutics, as opposed to an untested patient (i.e., a patient whose polymorphic status is unknown).

It is well known in the art that subjects with increased levels of HDL benefit from a reduced risk of developing a cardiovascular disorder. It is clearly shown by Applicants that subjects carrying the SNP 565 mutant allele have elevated levels of HDL as compared to subjects who carry the wild-type allele. See specification at page 12, lines 4-10 and 21-29; page 49, lines 12-14; page 50, lines 5-10; and especially Figures 9 and 11. Finally, it is shown that there is complete linkage disequilibrium between the 565 mutant allele and the 307 insertion. See specification at page 28, lines 28-30 and page 47, lines 25-28. Thus, it is quite clear that subjects testing positive for the presence of the 15bp insertion at 307 will be less likely to suffer from cardiovascular disease than subjects who do not carry the 307 insertion.

The Examiner points out that there is much uncertainty in the art. However, certainty is not what is required to enable the present claims. Statistically useful predictability is what is required. There are many diagnostic assays widely used in medicine today whose predictions are known to be much less than 100% accurate. Yet, as long as they provide sufficient value to the physician, they are useful until a better diagnostic tool is invented. It is submitted that Applicants have enabled their claims for the intended medical and experimental uses.

The Examiner further challenges Applicants demonstration of the linkage disequilibrium between the 565 allele and the 307 insertion. See the Office Action at page 13, line 19 to page

14, line 3. Applicants respectfully submit that this assertion is in error. There was 100% linkage disequilibrium shown in the 46 subjects tested. While it is possible that this high level of linkage disequilibrium will not be present in all patient populations, there is absolutely no evidence of this, and no reason to believe that it will be so. Factual statements made by Applicants are presumed to be accurate unless disproven by the Examiner. In the absence of specific evidence to the contrary, it is respectfully submitted that Applicants assertions must be accepted by the Examiner, and mere arguments to the contrary must be withdrawn.

The Examiner further challenges the correlation of the presence of the 565 mutant allele and high HDL levels in patients. Again, Applicants have provided clear data supporting this correlation, while the Examiner has not shown anything contradictory, other than an indication of unpredictability in the art (which as discussed earlier is baseless in relation to the presently claimed invention). It is respectfully submitted that the data provided by the Applicants (specification at page 12, lines 4-10 and 21-29; page 49, lines 12-14; page 50, lines 5-10; and especially Figures 9 and 11) has been more than adequately proven, and that absent specific data to the contrary, the Examiner must concede to Applicants conclusion that the presence of the mutant 565 allele (and thus the 307 insertion) correlates positively with the likelihood of high HDL levels in a patient.

In summary, Applicants have proven that the presence of the 307 insertion correlates completely with the presence of the mutant 565 allele; that the presence of the mutant 565 allele correlates strongly with the presence of elevated HDL levels in a patient; and it is well known to those skilled in the art that elevated levels of HDL correlate strongly with reduced risk of cardiovascular disease. Therefore, Applicants have fully enabled a method of predicting whether a patient has a modified susceptibility to a cardiovascular disorder by measuring the presence of the 307 insertion in the genome of the patient.

Thus, for the reasons detailed above, the Examiner is respectfully requested to withdraw the enablement rejection of claims 1-5 and 34-37.

Written Description Rejection

Claims 1-5 and 34-37 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter for which adequate written description was not provided. Applicants respectfully disagree and respectfully submit that this rejection is in error for the reasons provided below.

It is respectfully submitted that Applicants were in full possession of the presently claimed invention at the time of filing, and that this possession is demonstrated by a full, clear, concise and exact written description of the invention in the specification and claims as filed. The Examiner is correct that the sequences GAATGGAGGG and CTGCCAGGAAGAAGG are present in Genbank Sequence Accession No. M32997 (as shown in Figure 3). The Examiner is also correct that the sequence AGGGCCTGGC is not present in M32997. However, as Applicants clearly point out in the specification, the sequence AGGGCCTGGC is the first ten nucleotides of a 99 bp sequence that was erroneously omitted from M32997 (see page 28, lines 27-28). Thus, one would not expect to find the sequence AGGGCCTGGC in M32997. The sequence AGGGCCTGGC is provided by Applicants to show where the insertion 307 is located, by pointing out that insertion 307 occurs before this sequence (and after the sequence GAATGGAGGG). Therefore, Applicants have provided a clear and full written description of exactly what the insertion is (i.e., it is composed of the nucleotides CTGCCAGGAAGAAGG), and exactly where the insertion is present in the CTEP gene (i.e., it is after the sequence GAATGGAGGG, and before the sequence AGGGCCTGGC).

Additionally, the 99 bp region omitted by M32997 was known in the art prior to Applicant's filing of the present application (with its priority date of December 22, 2000). For example, in Genbank Sequence Accession No. AF210631, Agerholm-Larsen et al. report a partial nucleotide sequence from intron 12 of the CETP gene that includes the 5' flanking sequence provided by Applicants (i.e., GAATGGAGGG; see nucleotides 14-23 of AF210631), the 3' flanking sequence provided by Applicants (AGGGCCTGGC; see nucleotides 24-33 of AF210631), the 99 bp sequence omitted by M32997 (see nucleotides 24-122 of AF210631), as well as 13 nucleotides of the sequence after the 99bp omission (compare nucleotides 123-135 of AF210631 with nucleotides 658-670 of M32997). In this Genbank listing, it is stated that this sequence was submitted for publication (although apparently never published) on December 2, 1999. Similarly, in Genbank Sequence Accession No. AY008270, Travali et al. report 562 nucleotides of the CETP gene, including the 5' flanking sequence (GAATGGAGGG; see nucleotides 271-280 of AY008270), the 3' flanking sequence provided by Applicants (AGGGCCTGGC; see nucleotides 281-290 of AY008270), the 99 bp sequence omitted by M32997 (see nucleotides 281-379 of AY008270), as well as 183 nucleotides of the sequence after the 99bp omission (compare nucleotides 380-562 of AY008270 with nucleotides 658-840 of M32997). In this second listing, it is stated that this sequence was submitted for publication (although apparently never published) on September 20 and October 30, 2000. Copies of

AF210631 and AY008270 are attached. Thus, it is clear that the presence of the 99 bp missing from M32997 was already known to the art when Applicants filed the present application, and therefore Applicants description that the 15bp insertion (known as insertion 307) is placed between the sequences GAATGGAGGG and AGGGCCTGGC in the CETP gene provides a full, clear, concise and exact written description to demonstrate Applicants' possession of the presently claimed invention.

Thus, for the reasons detailed above, the Examiner is respectfully requested to withdraw the written description rejection of claims 1-5 and 34-37.

Conclusion

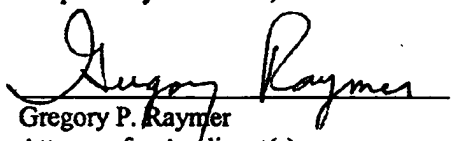
In view of the above, Applicants respectfully submit that all of the pending claims are allowable upon entry of the amendments submitted herewith, and that the application is otherwise in condition for allowance. The Examiner is respectfully requested to withdraw the objections and rejections of record, and, as the next official action, to provide a Notice of Allowance.

If any issues remain which can be resolved by a telephone conference, or should the Examiner have any questions or comments regarding this matter, the Examiner is respectfully invited to contact the undersigned at the telephone number shown below.

The Commissioner is hereby authorized to charge any additional fees required, or to credit any overpayment, to Deposit Account No. 16-1445.

Respectfully submitted,

Date: 5/13/04



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